REMARKS

Status of Claims

Upon entry of this amendment, claims 11-12, 21-22, 25-30, 33, 35-37, 39-48 are pending in the instant application. Claims 1-10, 13-20, 23-24, 31-32, 34, and 38 have been cancelled. Claims 11 and 12 have been amended. New claims 39-48 have been added. Applicants reserve the right to prosecute the cancelled subject matter, as well as the originally presented claims, in continuing applications. Support for the amendments to claims 11 and 12 is at least found at pages 8-11 of the as-filed application and Examples 2, 5, 6, 9-11, and Tables 1a, 1b, and 2. Accordingly, no new matter is added.

Election/Restrictions

The Examiner states that "the species election of malignant carcinoid has been withdrawn and extended to include previously non-elected specie as cited in the below prior art references, however not all of the non-elected specie are examined." Applicants respectively request that the Examiner make it clear on the record which species have been examined.

Information Disclosure Statement

The Examiner states that the IDS statements submitted on 10/25/05 (item C1) and 4/13/06 (C6) fail to comply because they are not publications. Items C1 and C6 correspond to International Search Report for PCT/US04/07144 and Supplementary European Search Report for EP 04 71 9198. Applicants confirm that the publications referred to these two search reports were submitted in the IDS statement concurrently with items C1 and C6.

Allowable Subject Matter

The Examiner has objected to claims 24, 31, and 33 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the limitations of the base claim and any intervening claims. Accordingly, Applicants have canceled claim 24 and rewritten the claim in independent form as new claim 39 including the limitations of claims the intervening claim 23 and base claim 12. Applicants have

canceled claim 31 and rewritten the claim in independent form as new claim 43 including the limitations of the base claim 12. Applicants have canceled claim 33 and rewritten the claim in independent form as new claim 46 including the limitations of the base claim 12.

§112 Rejection

Claim 11 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention. *See*, Office Action at page 3. Claim 38 has been canceled. Thus, the rejection is moot with respect to this claim. Applicants have amended claim 11 to recite the following cancers: leukemia, non-small cell lung cancer, CNS cancer, primary brain tumors, neuroblastoma, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. Applicants traverse the rejection as applied to the amended claims.

Nature of the Invention

With regard to the nature of the invention, the Examiner stated "the claim is directed to a method of treating cancer comprising administering to a mammal a therapeutically effective amount of a N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine dialeate *[sic]*." See, Office Action, page 4.

Claim 11 has been amended to specify the following cancers: leukemia, non-small cell lung cancer, CNS cancer, primary brain tumors, neuroblastoma, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. Thus, the amended claim does not encompass a method of treating cancer in general, but rather now is directed to a method of treating ten specific types of cancer.

State of the Prior Art:

The Examiner states that the state of the prior art related to cancer therapy remains highly unpredictable because various types of cancers have different causative agents involved in the cellular mechanism, which results in different treatment protocols. The Examiner cites Golub et al., Science Vol. 286, October 15, 1999, pages 531-537 as supporting the view that a current

challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types to maximize efficacy and minimize toxicity. The Examiner adds that cancer classification has also been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearances can follow significantly different clinical courses and show different responses to therapy. The Examiner contends that because of the obstacles stated above, one of skill in the art is prevented from accepting any therapeutic regimen related to cancer on its face, including the claimed subject matter. *See*, Office Action at page 4.

As amended the claims are now directed to ten types of cancer. Applicants assert that based on the numerous working examples in the instant application, which demonstrate the efficacy of the present invention against a wide range of diverse cancers, one skilled in the art is more than adequately enabled to both make and use the invention for the claimed cancers.

Further, it is well recognized under U.S. law that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as the predictability of the arts, but even in unpredictable arts, a disclosure of every operable species is not required. In re Marzocchi, 439 F.2d. 220, 223-224 (CCPA 1971); In re Fisher, 427 F.2d. 833, 839 (Fed. Cir. 1970). However, although a single embodiment may provide broad enablement in cases involving predictable factors, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species may not provide an adequate basis to support generic claims. In re Vickers, 141 F.2d. 522, 526-527 (CCPA 1944); In re Soll, 97 F.2d. 623, 624 (CCPA 1938). In cases involving unpredictable factors, more may be required. In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991); In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993); In re Fisher, 427 F.2d. at 839.

The instant specification discloses numerous operable species (*e.g.*, leukemia, non-small cell lung cancer, CNS cancer (primary brain tumors and neuroblastoma), melanoma, ovarian, renal, prostate, and breast cancer). Specifically, the efficacy of the present invention against the claimed cancers is demonstrated in a wide variety of different assays including inhibition of cell proliferation, apotosis, caspase activation, chick chorioallantoic membrane (CAM) assay, inhibition of cell growth, cord formation, and cell migration. For example, the anti-tumor effect of the present invention on 44 different cancer cell lines was measured. Multiple cell lines (the specific number for each is indicated in parentheses) were tested for each cancer i.e., leukemia (2), non-small cell lung (8), colon (5), CNS (4), melanoma (8), renal (8), prostate (2), and breast

(7). Several classical angiogenesis models were also used to evaluate potency of the present invention. For example, the chick chorioallantoic membrane (CAM) assay is one of the most widely used assays. The early chick embryo lacks a mature immune system and is therefore useful for studying tumor-induced angiogenesis. Eggs were dosed with compound followed by an incubation period. The eggs were then examined for viability and loss of vasculature. The inhibition of angiogenesis was based on the visual observation of the loss of generation of new blood vessels. See, Example 6 on page 25. A cord formation assay was used to assess the ability of the present invention to inhibit endothelial cells to form vessels *in vitro*. The effect of the compound (IC_{50}) was assessed compared to untreated controls by measuring the length of cords formed and number of junctions. See, Example 10 on page 33 and Table 8. The ability of the present invention to inhibit cell migration was assessed compared to untreated cells and IC_{50} values calculated. See, Example 11 on page 33 and Figure 10. Accordingly, Applicants assert that one skilled in the art is enabled to use the invention to treat cancer as now claimed.

Working Examples

The Examiner states that "although a wide claim to a vast variation of cancer treatment has been shown in the specification, it however fails to show how one such compound is capable of treating these wide variation *[sic]* of cancer. Noted these treatments are to cell lines, and animal models, Applicant has failed to show how these data is extrapolated for human studies. No supporting evidence have *[sic]* been provided." See, Office Action at page 5.

As amended, the claims are directed to ten types of cancer for which the instant specification is replete with working examples involving the use of the present invention to treat these ten types of cancers. Applicants submit that the skilled artisan readily and routinely utilizes the described *in vitro* tumor models (*e.g.*, apotosis, cell proliferation, cell migration and chord formation assays) when assaying the efficacy of anti-cancer compounds. Applicants submit that if an *in vitro* model is recognized as correlating to a specific condition, then the model should be accepted as a correlation unless the Examiner has evidence that the model does not correlate. Rigorous or exact correlation is not required. Merely a reasonable correlation based on the evidence as a whole is sufficient. See, *e.g.*, In re Brana, 34 USPQ2d 1436 (1995) holding that *in vitro* applications of the claimed methods, which reasonably correlate to *in vivo* treatment, are sufficient to support *in vivo* applications of the claim invention.

As discussed in detail above, the instant application contains numerous actual *in vitro* results. Forty-four different cell lines were tested and several angiogenic models were used. The use of cancer cell lines is still standard operating procedure for cancer research. Therefore, according to the holding in Brana, there is sufficient data to support Applicants' *in vivo* treatment claims.

Level of the Skilled Artisan

Applicants agree with the Examiner's assertion that the level of skill in the pharmaceutical arts is very high, but assert that one skilled in the art armed with the information provided in the specification could use the invention as now claimed without undue experimentation.

In view of the above, Applicants respectfully submit that amended claim 11 meets the enablement requirement of 35 U.S.C. §112, first paragraph for the treatment of cancer as claimed. Therefore, Applicants respectfully request that the rejection be withdrawn.

§103(a) Rejections (A and B)

A. Claims 11-12, 21-22, 25-30, 32, and 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rice et al. J. Heterocyclic Chem., 10(5):731-735 (1973)(referred to hereinafter as "Rice") taken with Mirabelli et al. Anti-Cancer Drug Design, 3(4):231-242 (1989)(referred to hereinafter as "Mirabelli") in view of Badger et al. U.S. Patent No, 5,602,166 (referred to hereinafter as "Badger") and Dagger et al. U.S. Patent No. 5,939,450 (referred hereinafter as "Dagger"). Applicants respectfully disagree.

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces that claimed invention; (2) there is a reason to combine the prior art references in such a way to achieve the claimed invention; and (3) the prior art reveals that in so making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

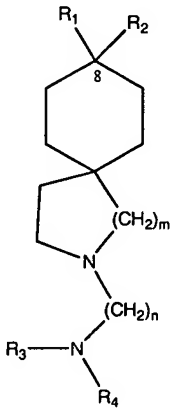
Applicants submit that a *prima facie* case of obviousness has not been established. To establish *prima facie* obviousness of a claimed invention, all of the claimed elements must be

taught or suggested by the prior art. M.P.E.P. § 2143.03. Withdrawal of the rejection is requested.

Rice

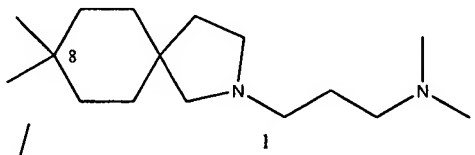
The Examiner states that "Rice et al. teach the drug N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane a member of the class of drugs azaspirane (see abstract) for the treatment of cancer where in the drug showed a significant inhibition of cancer cell growth in human cancer cells." See, Office Action at page 6. Applicants respectfully disagree. Applicants assert that Rice does not teach or suggest the compound, N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane, and further, Rice does not teach or suggest the specific types of cancer as-claimed in the instant invention.

The instant invention includes a method of treating ten types of cancers by administering to a mammal a therapeutically effective amount of an azaspirane compound, where the azaspirane is substituted at the 8-position with no less than a total of 5 carbon atoms. For example, the instant invention includes compounds of formula I,

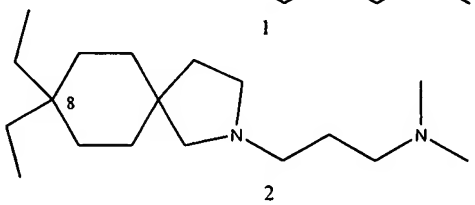


(I), where the total number of carbon atoms which comprise R_1 and R_2 is 5 or greater.

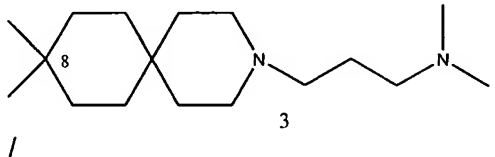
Rice does not disclose azaspirane compounds with a total number of 5 or more carbon atoms at the 8-position of the azaspirane ring. Rather, Rice discloses the four azaspirane compounds, **1**, **2**, **3**, and **4**, shown below.



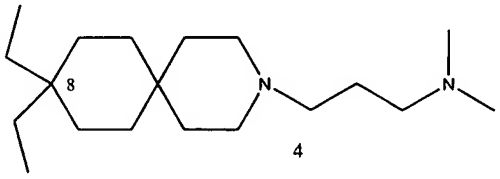
1



2



3



4

The Rice compounds have either two methyl substituents or two ethyl substituents at the 8-position of the azaspirane ring. These two substitution patterns provide a total of 2 carbon atoms and 4 carbon atoms respectively at the 8-position of the azaspirane ring. Unlike the compounds of the instant invention, none of the Rice compounds have a total of 5 or more carbon atoms at the 8-position of the azaspirane ring. There is no teaching or suggestion in Rice which would lead one skilled in the art to modify the Rice compounds to produce the compounds of the instant invention. Therefore, the Examiner's statement "Rice et al teach the drug N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane," a compound with two *propyl* (3-carbons each) substituents at the 8-position of the azaspirane ring, is incorrect. Rice does not teach or suggest this compound.

Applicants further submit that Rice does not teach the specific cancers claimed in the present invention. The present invention relates to a method of treating 10 specific types of cancer: leukemia, non-small cell lung cancer, CNS cancer, primary brain tumors, neuroblastoma, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. Support for these cancers is found throughout the instant specification. See, for example, pages 8-11 and Examples 2-3, 5, 6, 9-11 of the as-filed instant application. Whereas, Rice provides two sentences within the entire reference related to assaying the Rice compounds against cancer cells:

> Amines 1 and 3 as their dihydrochloride salts showed acute LD_{50} in range of 100-125 mg./kg. in rats. When the same compounds were assayed against human cancer cells grown in tissue culture, both 1 and 3 inhibited complete cancer cell growth at a concentration of 1×10^{-5} g./ml. Similar test evaluation for amines 2 and 4 is in progress.

See, Rice at page 732, paragraph 3 (the compound numbers referred to in this paragraph correspond to the structures shown above).

Rice provides no further details related to testing these compounds for anti-cancer activity. Rice does not provide any other disclosure related to cancer in the entire reference. Rice provides only a mere assertion by the authors that two of the compounds kill cancer cells. Based on this very limited reference to cancer in Rice with no experimental details, one of ordinary skill in the art can not ascertain what type of cancer was tested. Further, the skilled artisan would not have any basis to predict that the compounds of Rice would be useful for the claimed cancers.

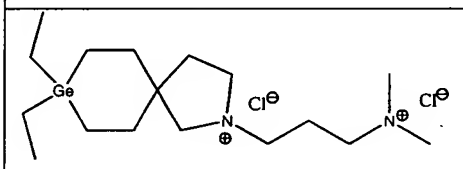
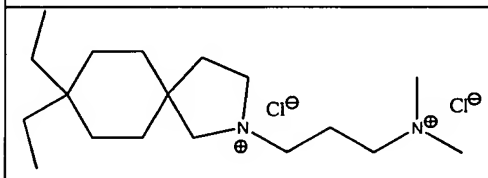
Therefore, it would not have been obvious to the skilled artisan to first, modify the compounds of Rice to produce instant compounds and second, to predict that the modified

compounds would be useful for the treatment of the ten cancers of the claimed invention. Accordingly, Applicants assert that Rice does not teach or suggest the claimed invention.

Mirabelli

Mirabelli does not cure the deficiencies of Rice. Rather, Mirabelli teaches compounds that are carbon analogues of the metal-containing compound, N,N-dimethylaminopropyl-2-aza-8,8-diethyl-8-germaspiro[4,5]decane i.e., the compounds of Mirabelli contain a carbon atom in place of the metal germanium. None of the compounds of Mirabelli contain a total of 5 or more carbon atoms at the 8-position of the azaspirane ring. As such, Mirabelli does not teach or suggest the compounds of the present invention.

Mirabelli compares the cytotoxicity of the metal-containing compound to its carbon analogues and merely shows that the carbon analogues are cytotoxic to HT-29 colon carcinoma cells. However, the carbon analogues are generally less potent than the metal-containing compound. For example, a comparison of the metal-containing compound to its direct analog in which the germanium metal is replaced by a carbon atom showed the carbon analog to be less potent:

Compound	IC_{50} (μM) to HT-29 cells
	12
	19

Because the carbon analogues, overall, in comparison to the metal-containing compound, were generally found to be less potent (See, table II of Mirabelli), Applicants assert that one of ordinary skill in the art would not predict that further modifications of the carbon analogues of Mirabelli would produce more potent anti-cancer compounds.

Further, Applicants submit that Mirabelli does not teach or suggest the claimed cancers i.e., leukemia, non-small cell lung cancer, CNS cancer, primary brain tumors, neuroblastoma, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. Rather, Mirabelli

shows that the carbon analogues are cytotoxic to HT-29 colon carcinoma cells. Mirabelli does not teach or suggest the claimed cancers.

The Examiner states that "Mirabelli teaches breast cancer and prostate cancer (see page 231)." See, Office Action at pages 6-7. Applicants disagree. The reference to breast (mammary adenocarcinoma) and prostate cancer (prostatic carcinoma) on page 231 in Mirabelli is made with respect to the anti-tumor activity of the metal-containing compound (N,N-dimethylaminopropyl)-2-aza-8,8-diethyl-8-germaspiro(4,5)decane. Applicants submit that Mirabelli does not teach or suggest that its carbon analogues would be effective for the treatment of breast or prostate cancer. Mirabelli does not test its carbon analogues against breast or prostate cancer cell lines or evaluate them in *in vivo* models related to these cancers. Further, one skilled in the art would not predict that the carbon analogues would be effective at treating breast and prostate cancer based on the results in Mirabelli, which showed that the replacement of the germanium metal with other atoms such as oxygen, sulfur, nitrogen, and silicon produced compounds that were significantly less potent than the metal-containing compound. In one instance, the compound even lost potency (*e.g.*, See, Table II in Mirabelli, specifically, compound **9** with an IC_{50} >1000 μM). These results show that it may be possible to replace the metal with a carbon atom and produce compounds which are cytotoxic. However, other substitutions for germanium do not yield the same reulsts. Thus, the skilled artisan would not have been able to predict that modifying the parent germanium compound by replacing the metal with these other atoms would have been successful.

Similarly, based on Mirabelli, the skilled artisan would not have been able to predict that the compounds of the instant invention would be useful for the treatment of leukemia. Mirabelli teaches away from the treatment of leukemia since none of the Mirabelli compounds demonstrated anti-tumor activity against leukemia. See, page 237, second paragraph of Mirabelli. In fact, the compounds of the instant invention have demonstrated anti-tumor effects on two different types of leukemia cells. See, Table 1a in as-filed application. Based on the results shown in Mirabelli as discussed above, it would not be possible for the skilled artisan to predict that the carbon analogues of Mirabelli would be effective for the treatment of breast and prostate cancer. Therefore, Applicants submit that the skilled artisan would not be motivated to modify the compounds of Mirabelli to produce the instant compounds and then use the modified compounds to treat breast or prostate cancer.

Badger

Badger does not cure the deficiencies of Rice or Mirabelli. Badger teaches a method of inhibiting cytokine production, particularly IL-1 and TNF by administering an azaspirane compound to a mammal. Badger does not teach a method of treating cancer. More specifically, Badger does not teach the claimed cancers. To the contrary, Badger lists at least 25 diseases/conditions which are exacerbated by IL-1 or TNF production and none of these are cancer. As such, Applicants assert that one of ordinary skill in the art reading Badger would not predict that azaspirane compounds which inhibit cytokine production would be useful for treating the claimed cancers. The Examiner has referenced Nakshatri et al as an example showing that the cytokine IL-1*a* is responsible for the induction of NF-kB activation in fibroblasts and the presence of IL-1 transcriptase in the majority of lymph node-positive breast cancer. The Examiner appears to be combining references in an attempt to provide a general rational as to why one of ordinary skill in the art would have combined the references. Nakshatri does not teach azaspirane compounds for the treatment of breast cancer. Further, Nakshatri does not teach *any* compounds for the treatment of breast cancer. Nakshatri does not teach a method of treating cancer. Nakshatri merely determines the presence of a cytokine transcript in the breast tissue. Nakshatri does not cure the deficiencies of Rice, Mirabelli, or Badger.

Dagger

Dagger does not cure the deficiencies of Rice, Mirabelli, or Badger. Rather, Dagger teaches the dimaleate salt of the azaspirane compound, N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine. Dagger notes the compound is useful as an immunomodulatory agent, particularly in the treatment of rheumatoid arthritis. Dagger does not teach a method of treating cancer. Dagger does not teach the claimed cancers. As such, Applicants assert that one of ordinary skill in the art would not predict that the compound of Dagger would be useful for the treatment of the claimed cancers.

B. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rice taken with Mirabelli, in view of Badger and Dagger as applied to claims 11-12, 21,22, 25-30, 32, 34-38 further in view of Gnaidecki et al. Expert Opinion Emerging Drugs (2002) 7(1) 69-90 (referred to

hereinafter as "Gnaidecki") taken with Victor J. Drugs in Dermatology 2002 1-15 (referred to hereinafter as "Victor"). Applicants disagree.

Gnaidecki and Victor do not cure the deficiencies of Rice, Mirabelli, Badger, and Dagger. The Examiner states that Gnaidecki teaches the use of atripod dimaleate (i.e., the dimaleate salt of N,N-diethyl-8,8-dipropyl-2-azaspiro[4,5]decane) in combination treatment for psoriasis. The Examiner also states that Victor teaches that levels of IL-1 increase in psoriatic lesions. The Examiner therefore contends that

because Badger teaches the inhibition of IL-1 by azaspirane compounds; and

because Victor teaches that IL-1 levels increase in psoriatic lesions; and

because Gnaidecki teaches that azaspirane compounds can be used in combination to treat psoriasis that it would have been obvious to the skilled artisan to use an azaspirane compound in combination to treat cancer. Applicants disagree.

Badger does not teach or suggest cancer. Badger does not teach or suggest the claimed cancers. Accordingly, Applicants assert that it would not be obvious to the skilled artisan to administer a compound of the invention with a chemotherapeutic or potentiating agent for the treatment of cancer. Further, the Office Action appears to be combining facts and attempting to provide a general rationale as to why one skilled in the art would have combined the references. The mere fact that the references can be combined or modified, however does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See M.P.E.P. §2143.01 (III). The Office Action merely combines facts and attempts to provide a motivation to combine the references without identifying the source of the motivation. The desirability of the combination is not suggested in any of the references cited by the Examiner. Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned remarks, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number provided below.

Respectfully submitted,

Dated: December 14, 2007

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